



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (HCT) to treat chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma in patients with markers of poor-risk disease to be **eligible for coverage**. (see Policy Guidelines and Rationale). Use of a myeloablative or reduced-intensity pretransplant conditioning regimen should be individualized based on factors that include patient age, the presence of comorbidities, and disease burden.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to treat chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) except as noted above to be **investigational**.*

Based on review of available data, the Company considers autologous hematopoietic cell transplantation (HCT) to treat chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) to be **investigational**.*

Policy Guidelines

STAGING AND PROGNOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA

Two scoring systems are used to determine stage and prognosis of patients with CLL or SLL. As outlined in Table PG1, the Rai and Binet staging systems classify patients into 3 risk groups with different prognoses and are used to make therapeutic decisions.

Table PG1. Rai and Binet Classification for CLL or SLL

Rai Stage	Risk	Description	Median Survival, y	Binet Stage	Description	Median Survival, y
------------------	-------------	--------------------	---------------------------	--------------------	--------------------	---------------------------

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

0	Low	Lymphocytosis	>10	A	≤3 lymphoid areas, normal hemoglobin and platelets	>10
I	Int	Lymphocytosis + lymphadenopathy	7-9	B	≥3 lymphoid areas, normal hemoglobin and platelets	7
II	Int	Lymphocytosis + splenomegaly ± lymphadenopathy	7-9			
III	High	Lymphocytosis + anemia ± lymphadenopathy or splenomegaly	1.5-5	C	Any number of lymphoid areas, anemia, thrombocytopenia	5
IV	High	Lymphocytosis + thrombocytopenia ± anemia, splenomegaly, or lymphadenopathy	1.5-5			

CLL: chronic lymphocytic leukemia; Int: Intermediate; SLL: small lymphocytic lymphoma.

Because prognoses of patients vary within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management. They are summarized in Table PG2, according to availability in clinical centers.

Table PG2. Markers of Poor Prognosis in CLL or SLL

Community Center	Specialized Center
<ul style="list-style-type: none"> Advanced Rai or Binet stage Male sex Atypical morphology or CLL or SLL Peripheral lymphocyte doubling time <12 mo CD38-positive Elevated β₂-microglobulin level Diffuse marrow histology Elevated serum lactate dehydrogenase level Fludarabine resistance 	<ul style="list-style-type: none"> IgVh wild type Expression of ZAP-70 protein Del(11q22-q23) (loss of <i>ATM</i> genet) del(17p13)/variant <i>TP53</i> Trisomy 12 Elevated serum CD23 Elevated serum tumor necrosis factor-α Elevated serum thymidine kinase

CLL: chronic lymphocytic leukemia; IgVh: immunoglobulin heavy-chain variable-region; SLL: small lymphocytic lymphoma.

An expert panel convened by the American Society for Blood and Marrow Transplantation was queried about criteria used to define high-risk CLL, as part of the process for developing 2016 guidelines. Panelists responded that criteria are presence of del17P and/or *TP53* variants (100%) and presence of complex karyotype (67%).

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered as candidates for reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-HCT). They include those patients whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allo-HCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC before a second allo-HCT if complete remission could be reinduced with chemotherapy.

The ideal allogeneic donors are human leukocyte antigen (HLA)–identical siblings, matched at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Related donors mismatched at a single locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, haploidentical donors—typically a parent or a child of the patient—with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens, have been under investigation as a stem cell source. Most patients will have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Background/Overview

CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA

CLL and SLL are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well-differentiated morphology. In CLL, these cells accumulate in blood, bone marrow, lymph nodes, and spleen; in SLL they are generally confined to lymph nodes. The Revised European-American/World Health Organization Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.

CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other, respectively. Both tend to present as asymptomatic enlargement of the lymph nodes, tend to be indolent in nature, but can undergo transformation to a more aggressive form of disease (eg, Richter transformation). The median age at diagnosis of CLL is approximately 72 years, but it may present in younger individuals, often as poor-risk disease with significantly reduced life expectancy.

Treatment regimens used for CLL are generally the same as those used for SLL, and treatment outcomes are comparable for both diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses, with median survivals of 6 to 10 years; however, the median survival of high-risk CLL or SLL may only be 2 years. Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy, and nearly all patients ultimately die of their disease. This natural disease history prompted investigation of HCT as a possible curative regimen.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

HEMATOPOIETIC CELL TRANSPLANTATION

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allo-HCT. Compatibility is established by typing of HLA using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for HCT

Conventional Conditioning for HCT

The conventional practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. The slower GVM effect is considered the potentially curative component, but it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

Reduced-Intensity Conditioning for Allo-HCT

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow-mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

POLICY GUIDELINES

STAGING AND PROGNOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA

Two scoring systems are used to determine stage and prognosis of patients with CLL or SLL. As outlined in Table PG1, the Rai and Binet staging systems classify patients into 3 risk groups with different prognoses and are used to make therapeutic decisions.

Table PG1. Rai and Binet Classification for CLL or SLL

Rai Stage	Risk	Description	Median Survival, y	Binet Stage	Description	Median Survival, y
0	Low	Lymphocytosis	>10	A	≤3 lymphoid areas, normal hemoglobin and platelets	>10
I	Int	Lymphocytosis + lymphadenopathy	7-9	B	≥3 lymphoid areas, normal hemoglobin and platelets	7
II	Int	Lymphocytosis + splenomegaly ± lymphadenopathy	7-9			
III	High	Lymphocytosis + anemia ± lymphadenopathy or splenomegaly	1.5-5	C	Any number of lymphoid areas, anemia, thrombocytopenia	5
IV	High	Lymphocytosis + thrombocytopenia ± anemia, splenomegaly, or	1.5-5			

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

lymphadenopathy

CLL: chronic lymphocytic leukemia; Int: Intermediate; SLL: small lymphocytic lymphoma.

Because prognoses of patients vary within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management. These are summarized in Table PG2, according to availability in clinical centers.

Table PG2. Markers of Poor Prognosis in CLL or SLL

Community Center	Specialized Center
<ul style="list-style-type: none"> Advanced Rai or Binet stage Male sex Atypical morphology or CLL or SLL Peripheral lymphocyte doubling time <12 mo CD38⁺ Elevated β_2-microglobulin level Diffuse marrow histology Elevated serum lactate dehydrogenase level Fludarabine resistance 	<ul style="list-style-type: none"> IgVh wild type Expression of ZAP-70 protein Del(11q22-q23) (loss of <i>ATM</i> gene) del(17p13)/variant <i>TP53</i> Trisomy 12 Elevated serum CD23 Elevated serum tumor necrosis factor-α Elevated serum thymidine kinase

CLL: chronic lymphocytic leukemia; IgVH: immunoglobulin heavy-chain variable-region; SLL: small lymphocytic lymphoma.

An expert panel convened by the American Society for Blood and Marrow Transplantation was queried about criteria used to define high-risk CLL, as part of the process for developing 2016 guidelines. Panelists responded that criteria are presence of del17P and/or *TP53* mutations (100%) and presence of complex karyotype (67%).

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered as candidates for RIC allo-HCT. They include those patients whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allo-HCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC before a second allo-HCT if a complete remission could be reinduced with chemotherapy.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Related donors mismatched at 1 locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, haploidentical donors—typically a parent or a child of the patient—with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens, have been under investigation as a

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

stem cell source. Most patients will have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under the Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic cells are included in these regulations.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The original review was based on 2 TEC Assessments, 1 from 1999 that examined autologous HCT for CLL and SLL; the other from 2002 on allogeneic HCT (allo-HCT) to treat CLL and SLL. Both assessments indicated that existing data were insufficient to permit scientific conclusions on the use of either procedure, and were limited by interstudy heterogeneity in patients' baseline characteristics, procedural differences, sample size, and short follow-up. A direct comparative analysis from the International Bone Marrow Transplant Registry commissioned by TEC in 2002 to analyze allo-HCT results was insufficient to permit scientific conclusions on the net health outcome of this procedure for relapsed or refractory CLL or SLL.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

Subsequent reviews through 2008 have discussed uncertainties concerning the type of transplant (autologous vs allogeneic), the intensity of pretransplant conditioning, the optimal timing of transplantation in the disease course, the baseline patient characteristics that best predict likelihood of clinical benefit from transplant, and the long-term risks of adverse outcomes. The conclusions reached at that time suggested that, although autologous HCT may prolong survival in select patients with CLL or SLL (eg, those with chemotherapy-sensitive malignancy who had a good response to front-line therapy and were transplanted early in the course of disease), it had not yet been shown to be curative.

ALLOGENEIC HCT

Data compiled in review articles through 2012 suggested that myeloablative allo-HCT has curative potential for CLL or SLL. Long-term disease control (33%-65% overall survival [OS] at 3-6 years) due to a low rate of late recurrences has been observed in all published series, regardless of donor source or conditioning regimen. However, high rates (24%-47%) of treatment-related mortality discourage this approach in early- or lower risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning.

The development of reduced-intensity conditioning regimens has extended the use of allo-HCT to older or less fit patients who account for the larger proportion of this disease than younger patients, as outlined in two 2009 review articles. Six published nonrandomized studies involved a total of 328 patients with advanced CLL who underwent reduced-intensity conditioning allo-HCT using regimens that included fludarabine in various combinations including cyclophosphamide, busulfan, rituximab, alemtuzumab, and total body irradiation. Most patients in these series were heavily pretreated, with a median of 3 to 5 courses of prior regimens. Among individual studies, 27% to 57% of patients had the chemotherapy-refractory disease, genetic abnormalities including a 17p13 deletion, 11q22 deletion, and *VH* unmutated, or a combination of those characteristics. A substantial proportion in each study (18%-67%) received stem cells from a donor other than a human leukocyte antigen-identical sibling. Reported nonrelapse mortality associated primarily with graft-versus-host disease and its complications ranged from 2% at 100 days to 26% overall at median follow-up ranging from 1.7 to 5 years. OS rates ranged from 48% to 70% at follow-up that ranged from 2 to 5 years. Similar results were reported for progression-free survival (PFS), which was 34% to 58% at 2- to 5-year follow-up. Very similar results were reported from a phase 2 study published in 2010 evaluating use of reduced-intensity conditioning allo-HCT in patients (n=90; median age, 53 years; range, 27-65) with poor-risk CLL, defined as having one of the following: refractoriness or early relapse (ie, <12 months) after purine-analogue therapy; relapse after autologous HCT; or progressive disease in the presence of an unfavorable genetic marker (11q or 17p deletion, and/or unmutated immunoglobulin heavy-chain variable-region status and/or usage of the *VH3-21* gene). With a median follow-up of 46 months, 4-year NRM, event-free survival (EFS), and OS rates were 23%, 42%, and 65%, respectively. EFS estimates were similar for all genetic subsets, including those with a 17p deletion.

Section Summary: Allogeneic HCT

No RCTs evaluating allo-HCT in patients with CLL were identified. Data from nonrandomized studies found OS rates between 48% and 70% at 2 to 5 years and PFS rates of 34% to 58% at 2 to 5 years after allo-HCT

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

for poor-risk CLL. Despite not being randomized, these studies suggest that allo-HCT can provide long-term disease control and OS in patients with poor-risk CLL and SLL.

AUTOLOGOUS HCT

A 2015 systematic review of autologous HCT as the first-line consolidation in CLL included a literature search through November 2014. Four RCTs in adults were selected. Outcomes included OS, PFS, EFS, and harms (adverse events, treatment-related mortality, secondary malignancies). In these 4 trials, 301 patients were randomized to the autologous HCT arm and 299 to the control arm using first-line therapy without HCT as consolidation. Autologous HCT did not result in a statistically significant improvement in OS (hazard ratio, 0.91; 95% confidence interval [CI], 0.62 to 1.33) or in PFS (hazard ratio, 0.70; 95% CI, 0.32 to 1.52). There was a statistically significant improvement in EFS favoring autologous HCT (hazard ratio, 0.46; 95% CI, 0.26 to 0.83). A higher rate of secondary malignancy or treatment-related mortality was not associated with autologous HCT.

A phase 3 European Intergroup RCT (2011) evaluated autologous HCT as second- or third-line treatment of CLL. The trial compared autologous HCT (n=112) with postinduction observation (n=111) for consolidation in patients with CLL who achieved a complete response (59% of total) or very good partial response (27% of total) following fludarabine-containing induction therapy. Overall, patients' age ranged from 31 to 65 years, and they presented with Binet stage A progressive (14%), B (66%), and C (20%) disease. The population either did not have a 17p deletion or 17p deletion status was unknown. Median EFS (the primary outcome) was 51 months (range, 40-62 months) in the autograft group and 24 months (range, 17-32 months) in the observation group; 5-year EFS rates were 42% and 24%, respectively (p<0.001). The relapse rate at 5-year follow-up was 54% in the autograft group and 76% in the observational group (p<0.001); median time to relapse requiring therapy or to death (whichever came first) was 65 months (range, 59-71 months) and 40 months (range, 25-56 months), respectively (p=0.002). OS probability at 5-year follow-up was 86% (95% CI, 77% to 94%) in the autograft arm and 84% (95% CI, 75% to 93%) in the observation arm (p=0.77), with no evidence of a plateau in the areas under the curve. There was no significant difference in nonrelapse mortality between groups (4% for autologous HCT vs 0% for observation; p=0.33). The myelodysplastic syndrome was observed at follow-up in 3 patients receiving an autograft and in 1 patient in the observational group.

In a subsequent 2014 report, authors of the European Intergroup RCT presented quality of life (QOL) findings from this trial. Two secondary analyses were performed to investigate the impact of HCT and relapse on QOL. In the primary analysis, the authors demonstrated an adverse impact of HCT on QOL, which was largest at 4 months and continued throughout the first year after randomization. Further, a sustained adverse impact of relapse on QOL was observed, which worsened over time. Thus, despite better disease control by autologous HCT, the side effects turned the net effect toward inferior QOL in the first year and comparable QOL in the following 2 years after randomization.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

Section Summary: Autologous HCT

A systematic review of RCTs did not find that autologous HCT as first-line consolidation therapy for CLL significantly improved OS or PFS compared with alternative treatments. An RCT evaluating autologous HCT as second- or third-line treatment of CLL did not find that HCT improved the net health outcome.

SUMMARY OF EVIDENCE

For individuals who have CLL/SLL and markers of poor-risk disease who receive allo-HCT, the evidence includes single-arm prospective and registry-based studies as well as a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Data have suggested that allo-HCT can provide long-term disease control and overall survival in patients with poor-risk CLL/SLL. High rates of treatment-related morbidity discourage this approach in lower risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CLL/SLL who receive autologous HCT, the evidence includes randomized controlled trials, systematic reviews, and a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Autologous HCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. Studies of autologous HCT published to date have not shown improvement in overall survival in patients with CLL/SLL, and results must be considered in the context of improved outcomes with the use of newer chemoimmunotherapy agents. Furthermore, evidence from the European Intergroup randomized controlled trial has suggested the quality of life issues are important in selecting patients for autologous HCT and may dictate the management course for patients who are otherwise candidates for this approach. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma", 8.01.15, 1:2018.
2. Blue Cross and Blue Shield Association (TEC). High-dose chemotherapy with autologous stem cell support for chronic lymphocytic leukemia/small lymphocytic lymphoma. TEC Assessments. 1999;Volume 14:Tab 20.
3. Blue Cross and Blue Shield Association (TEC). High-dose chemotherapy plus allogeneic stem cells to treat chronic lymphocytic leukemia or small lymphocytic lymphoma. TEC Assessments. 2002;Volume 17:Tab 4.
4. Abbott BL. Chronic lymphocytic leukemia: recent advances in diagnosis and treatment. *Oncologist*. Jan 2006;11(1):21-30. PMID 16401710
5. Brugiatelli M, Bandini G, Barosi G, et al. Management of chronic lymphocytic leukemia: practice guidelines from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. *Haematologica*. Dec 2006;91(12):1662-1673. PMID 17145603
6. Dreger P, Brand R, Michallet M. Autologous stem cell transplantation for chronic lymphocytic leukemia. *Semin Hematol*. Oct 2007;44(4):246-251. PMID 17961723
7. Gine E, Moreno C, Esteve J, et al. The role of stem-cell transplantation in chronic lymphocytic leukemia risk-adapted therapy. *Best Pract Res Clin Haematol*. Sep 2007;20(3):529-543. PMID 17707838
8. Gribben JG. Role of allogeneic hematopoietic stem-cell transplantation in chronic lymphocytic leukemia. *J Clin Oncol*. Oct 2008;26(30):4864-4865. PMID 18794537

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

9. Kharfan-Dabaja MA, Anasetti C, Santos ES. Hematopoietic cell transplantation for chronic lymphocytic leukemia: an evolving concept. *Biol Blood Marrow Transplant.* Apr 2007;13(4):373-385. PMID 17382245
10. Gladstone DE, Fuchs E. Hematopoietic stem cell transplantation for chronic lymphocytic leukemia. *Curr Opin Oncol.* Mar 2012;24(2):176-181. PMID 22234253
11. Delgado J, Milligan DW, Dreger P. Allogeneic hematopoietic cell transplantation for chronic lymphocytic leukemia: ready for prime time? *Blood.* Sep 24 2009;114(13):2581-2588. PMID 19641189
12. Dreger P. Allogeneic transplantation for chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program.* 2009:602-609. PMID 20008245
13. Brown JR, Kim HT, Li S, et al. Predictors of improved progression-free survival after nonmyeloablative allogeneic stem cell transplantation for advanced chronic lymphocytic leukemia. *Biol Blood Marrow Transplant.* Oct 2006;12(10):1056-1064. PMID 17084369
14. Delgado J, Thomson K, Russell N, et al. Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. *Blood.* Feb 15 2006;107(4):1724-1730. PMID 16239425
15. Dreger P, Brand R, Hansz J, et al. Treatment-related mortality and graft-versus-leukemia activity after allogeneic stem cell transplantation for chronic lymphocytic leukemia using intensity-reduced conditioning. *Leukemia.* May 2003;17(5):841-848. PMID 12750695
16. Khouri IF, Saliba RM, Admirand J, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable expression of ZAP-70 in refractory chronic lymphocytic leukaemia. *Br J Haematol.* May 2007;137(4):355-363. PMID 17456058
17. Schetelig J, Thiede C, Bornhauser M, et al. Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. *J Clin Oncol.* Jul 15 2003;21(14):2747-2753. PMID 12860954
18. Sorror ML, Storer BE, Sandmaier BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *J Clin Oncol.* Oct 20 2008;26(30):4912-4920. PMID 18794548
19. Dreger P, Dohner H, Ritgen M, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. *Blood.* Oct 7 2010;116(14):2438-2447. PMID 20595516
20. Reljic T, Kumar A, Djulbegovic B, et al. High-dose therapy and autologous hematopoietic cell transplantation as front-line consolidation in chronic lymphocytic leukemia: a systematic review. *Bone Marrow Transplant.* Aug 2015;50(8):1144. PMID 26242579
21. Michallet M, Dreger P, Sutton L, et al. Autologous hematopoietic stem cell transplantation in chronic lymphocytic leukemia: results of European intergroup randomized trial comparing autografting versus observation. *Blood.* Feb 3 2011;117(5):1516-1521. PMID 21106985
22. de Wreede LC, Watson M, van Os M, et al. Improved relapse-free survival after autologous stem cell transplantation does not translate into better quality of life in chronic lymphocytic leukemia: lessons from the randomized European Society for Blood and Marrow Transplantation-Intergroup study. *Am J Hematol.* Feb 2014;89(2):174-180. PMID 24123244
23. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* Nov 2015;21(11):1863-1869. PMID 26256941
24. Kharfan-Dabaja MA, Kumar A, Hamadani M, et al. Clinical practice recommendations for use of allogeneic hematopoietic cell transplantation in chronic lymphocytic leukemia on behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* Dec 2016;22(12):2117-2125. PMID 27660167
25. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: chronic lymphocytic leukemia/small lymphocytic lymphoma. Version 1.2017. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed December, 2016.

Policy History

Original Effective Date: 01/28/2002

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

Current Effective Date: 09/19/2018

12/06/2001 Medical Policy Committee review

01/28/2002 Managed Care Advisory Council approval

06/24/2002 Format revision. Coverage eligibility policy unchanged.

03/31/2004 Medical Director review

04/20/2004 Medical Policy Committee review. Format revision.

04/26/2004 Managed Care Advisory Council approval

06/03/2005 Medical Director review

06/21/2005 Medical Policy Committee review. Format revision. Rationale and Source added.

07/15/2005 Managed Care Advisory Council approval

07/07/2006 Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.

08/01/2007 Medical Director review

08/15/2007 Medical Policy Committee approval. Rationale/Source updated. Coverage eligibility unchanged.

08/06/2009 Medical Policy Committee approval.

08/26/2009 Medical Policy Implementation Committee approval. Rationale/Source updated. Coverage eligibility unchanged. Title changed.

07/01/2010 Medical Policy Committee approval.

07/21/2010 Medical Policy Implementation Committee approval. Policy statement regarding allogeneic transplant in patients with markers of poor-risk disease changed; now may be considered medically necessary.

07/07/2011 Medical Policy Committee approval.

07/20/2011 Medical Policy Implementation Committee approval. No change to coverage.

06/28/2012 Medical Policy Committee review

07/27/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

03/04/2013 Coding updated

08/01/2013 Medical Policy Committee review

08/21/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

09/04/2014 Medical Policy Committee review

09/17/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

09/03/2015 Medical Policy Committee review

09/23/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

09/08/2016 Medical Policy Committee review

09/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

09/07/2017 Medical Policy Committee review

09/20/2017 Medical Policy Implementation Committee approval. The word stem was removed from title and body of the policy.

09/06/2018 Medical Policy Committee review

09/19/2018 Medical Policy Implementation Committee approval. Added policy guidelines.

Next Scheduled Review Date: 09/2019

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052
Original Effective Date: 01/28/2002
Current Effective Date: 09/19/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT)[®]†, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	C91.10-C91.12 C91.30-C91.32 C91.50-C91.52 C91.60-C91.62 C91.90-C91.92 C91.A0-C91.A2 C91.Z0-C91.Z2

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052

Original Effective Date: 01/28/2002

Current Effective Date: 09/19/2018

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

† Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.